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June 1, 2008.



To : Dr. Yelena G. Gakh
US patent & Trademark Office
PO Box 1450
Alexandria, VA 22313-1450

Re : Application No. 10/675,765
Art Unit 1743

Dear Dr. Yelena G. Gakh :

We acknowledge the receipt of the Office letter dated 03/27/2008 and would like to respond to the letter as follows :

1. Objection of claim 33.

We would like to amend claim 33 in a way to further limit the subject matter of claim 31. This limitation refers to only small organic chemicals having a hydroxyl group with molecular mass less than 1000 atomic mass unit. The claim is amended by addition of underlined phrase and deletion of words in double brackets

2. Claim rejections

We would like to clarify a perception of the Office that the invention provides a method for the analysis of an "unknown alcohol" in a sample and, because the structure of the alcohol is unknown, the structure of the synthesized internal standard is also "unknown". The fact is quite the opposite. The invention provides a method of analysis of alcohol by mass spectrometry which includes identification of the specific mass ions of the alcohol (both molecular ion and daughter ion) and quantification of these ions to provide concentration of the alcohol in a sample. The chemical structure of the alcohol and, therefore its molecular mass, must be "known" before the analysis so that both molecular ion and daughter ion can be input into the mass spectrometer for measurement. The invention provides an example of the analysis of Naltrexone in human plasma sample, a pharmaceutical compound having an alcoholic group. From the "known" chemical structure of Naltrexone, we can determine that the molecular mass of Naltrexone is 341. Naltrexone purchased from a commercial source was used to synthesized the internal standard Naltrexone acetate ester-d3 (step 1 of the example) whose structure is also "known" from the synthesis. From the chemical structure of Naltrexone acetate ester-d3, we can determine that its molecular mass is 386 and set the mass spectrometer to collect signal at M+1 (positive mode) at 387 (step 2). This molecular mass ion 387 fragments to its daughter mass ion 369.2 (step2). Naltrexone in a sample is identified by a mass combination of 387.0>369.2. Measurement of the signal response of this mass combination is used to calculate the concentration of Naltrexone.

The method of the invention can be further clarified by a comparison with the method of analysis of alcohol provided by the Office from 4 different groups: Johnson,

Esteban, Dufour, and Pyon. A table of method is made for easy comparison as follows :

	Johnson	Esteban et al.	Dufour et al.	Pyon et al.	This invention
Representative alcohol	Tetradecanol	Glucose	Phenylethanol	Dimethylphenol	Naltrexone
Internal standard	Tetradecanol-d29	Glucose-6C13	Phenylethanol-d2	Dimethylphenol-d3	Naltrexone acetate ester-d3
Derivatizing reagent for alcohol	DMG	none	none	BSTFA	Acetic anhydride
isolated alcohol	DMG tetradecanol	Glucose	Phenylethanol	BSTFA Dimethylphenol	Naltrexone acetate ester
Derivatizing reagent for internal standard	DMG	none	none	BSTFA	Acetic anhydride-d6
isolated internal standard	DMG tetradecanol-d29	Glucose-6C13	Phenylethanol-d2	BSTFA Dimethylphenol-d3	Naltrexone acetate ester-d3
Sample matrix	Human urine	Human serum	Beer	Rat urine	Human plasma

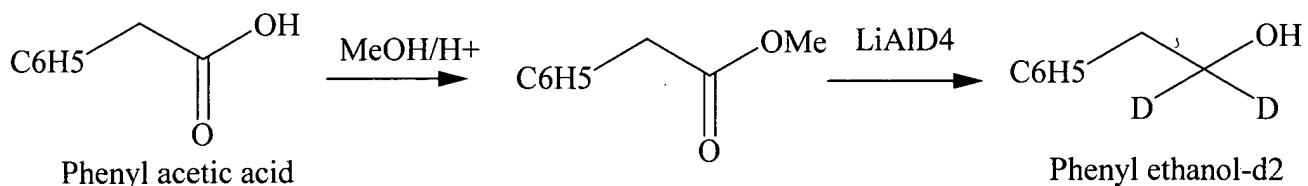
From the table it can be seen that all 4 groups made use of “isotopically labeled alcohol” in the analysis of alcohol while this invention did not. The use of “isotopically labeled alcohol” as internal standard and the preparation of its labeled derivatized alcohol using non-labeled derivatizing reagent is considered prior art as demonstrated by Johnson and Pyon. However, the use of “non-labeled alcohol” and a “labeled derivatizing reagent” to prepare labeled internal standard in this invention is not known in prior art. A close look at Johnson’s work reveals that Tetradecanol-d29 was prepared from Tetradecanoic acid, not from Tetradecanol. Also in Dufour’s work, Phenylethanol-d2 was prepared from Phenyl acetic acid, not Phenylethanol.

In the Office letter, the phrase “It would have been obvious for a person of ordinary skill in the art to modify Johnson’s method by utilizing internal standards prepared from isotopically labeled analytes, as taught by Esteban, Dufour or Pyon for isotope dilution mass spectrometry” was quoted to reject our claims. We ask that the Office re-considers our claims because it is clearly shown in our method that the utilized internal standard was not prepared from isotopically labeled analytes. In our example of analysis of Naltrexone, the utilized internal standard Naltrexone acetate ester-d3 was prepared from the non-labeled Naltrexone (see step1 of the example). Deuterium label came from acetic anhydride-d6, the labeled derivatizing reagent. Johnson did

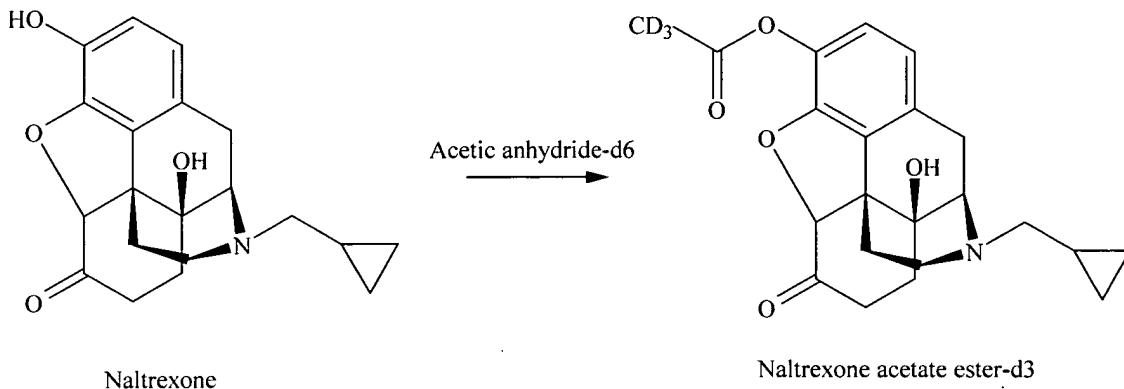
not make use of “labeled DMG” for the preparation of DMG-tetradecanol-d29. Pyon did not use “labeled BSTFA” for the preparation of BSTFA-Dimethylphenol-d3. Except for Esteban and Pyon who purchased stable isotope labeled alcohols from a commercial source, Johnson and Dufour presented the syntheses of isotopically labeled alcohol from the carboxylic acid precursors.



Johnson's synthesis of Tetradecanol-d29 page 279



Dufour's synthesis of Phenylethanol-d2 page 89



The method of this invention shows that the isotopically labeled internal standard is synthesized from the alcohol while Johnson and Dufour synthesized their isotopically labeled alcohol from the acid precursor. The convenience and simplicity of the method is clearly demonstrated here. Authentic alcohol is required for the construction of the calibration curve in any alcohol analysis. The method of this invention shows that this authentic alcohol can be used to prepare isotopically labeled internal standard without searching for the precursor acid which in many cases, may not be available commercially. In determining the scope and contents of the prior art, a person of ordinary skill in the art can surely ascertain the difference between the

prior art and the claims at issue. The above syntheses are considered objective evidence for the non-obviousness of the method of this invention.

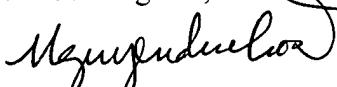
In the Office letter, you mention the phrase "Because it is so advantageous to use the deuterated analogue of the analyte as the internal standard, it is beneficial to synthesize the deuterated analogue if it is unavailable commercially". It certainly was not the case in Pyon's work where deuterated MBA (4-methylbenzyl alcohol) was not commercially available. The author had to use DMP-d3 for the analysis of MBA. It might be possible that the synthesis of deuterated MBA was not straightforward for the author at that time. Had Pyon used the method of this invention for the analysis of DMP and MBA, he could have had deuterated internal standards for both. The deuterated internal standard for DMP can be synthesized from DMP and the deuterated internal standard for MBA can be synthesized from MBA using the method of this invention. The key difference between the method of this invention and prior art of analysis of alcohol by mass spectrometry is the ability of this method to allow chemist to synthesize the isotope labeled internal standard from the authentic sample of the alcohol itself, using the similar method of derivatizing the alcohol.

Because the synthesis of stable isotope labeled derivatized alcohol is essential for our method of analysis of alcohol and the derivatization of the alcohol in samples is required, we ask the office to allow us to amend claim 31 in such a way to reflect this matter without introducing new matter. Claim 31 is now rephrased as "A method of synthesis of stable isotope labeled internal standard and additional derivatizing reaction in the identification and quantification of alcohol in a sample by mass spectrometry consisting the steps of....". The phrase "stable isotope labeled" is added to this claim to further clarified the nature of the ester internal standard.

Claim 35 presents how the ester internal standard is made from the alcohol and the labeled derivatizing reagent. This procedure is not included in Claim 31. Claim 42 states a fact that the ester internal standard cannot react with the derivatizing reagent that derivatizes the alcohol in the sample. This is not a condition for derivatizing the alcohol in the sample. It states the limitation of the labeled ester internal standard.

The method of this invention was shown to be different from the scope and content of prior art as exemplified by the works of the above authors. The advantages of the method of this invention are ascertained in terms of economy, convenience, and simplicity. People of ordinary skill in this art of analysis can easily recognize the nonobviousness of the method. We ask the Office to allow the claims as presented.

Kindest regards,



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